AMENDMENTS TO THE SPECIFICATION

Amend the paragraph beginning on page 3, line 11 of the specification as follows.

Suitable sustained release polymers include, e.g., amino methacrylate copolymers (~~Eudragit~~ EUDRAGIT® RL, ~~Eudragit~~ EUDRAGIT® RS), ethylcellulose or hydroxypropyl methylcellulose. In some embodiments, the methacrylic acid copolymer is a pH dependent anionic polymer solubilizing above pH 5.5. The methacrylic acid copolymer can be provided as a dispersion and be present in the composition at a concentration of 10-20% wt/wt. A preferred methacrylic acid copolymer is EUDRAGIT® L 30 D-55.

Amend the paragraph beginning on page 3, line 17 of the specification as follows.

In preferred embodiments, the enteric coated tablet dosage form includes IL-11, a filler microcrystallinecellulose (~~Avicel~~ AVICEL® PH 102), a disintegrant ~~Explotab~~ EXPLOTAB®, a buffer sodium phosphate, an antioxidant methionine, a surfactant ~~Tween~~ TWEEN 80™, a lubricant magnesium stearate and an enteric coat .

Amend the paragraph beginning on page 3, line 21 of the specification as follows.

In a preferred embodiment, the sustained release tablet dosage form that includesIL-11, fillers (e.g., microcrystallinecellulose (~~Avicel~~ AVICEL® PH 102) and sucrose), a matrix forming polymer (hydroxypropylmethylcellulose ~~Methocel~~ METHOCEL™ K4M Prem, ~~Methocel~~ METHOCEL™ K100 LV, LH, CR, Premium), a glidant (such as ~~Syloid~~ SYLOID®), a buffer sodium phosphate, an antioxidant methionine, a surfactant (such as ~~Tween~~ TWEEN 80™), and a lubricant (such as magnesium stearate).

Amend the paragraph beginning on page 7, line 28 of the specification as follows.

A schematic diagram showing a preferred multiparticulate IL-11 formulation is shown in FIG. 1. On to a central sugar sphere is disposed a layer containing rhIL-11. This rhIL-11 drug layer in turn is covered with a hydroxypropyl methylcellulose (HPMC) sealing coat. This HPMC sealing coat is covered with a methacrylic acid copolymer (e.g., with ~~Eudragit~~ EUDRAGIT® L20D-55) enteric coat, and the entire pellet is covered with a second or final HPMC sealing coat.

Amend the paragraph beginning on page 8, line 11 of the specification as follows.

The flow diagram illustrates that sugar spheres are loaded onto a fluid-bed coater and coated with a drug layer that includes rhIL-11, sodium phosphate dibasic, sodium phosphate monobasic, glycine, polysorbate 80, methionine, hydroxypropyl methylcellulose (HPMC), and purified water to form a coat. An enteric coat is applied containing ~~Eudragit~~ EUDRAGIT®, talc, sodium hydroxide, triethyl citrate, and purified water. A seal coat of HPMC and purified water is then applied followed by talc as an anti-static agent. Subsequent processing can include, e.g., storage for 180 days at 2-8 degrees Centigrade.

Amend the paragraph beginning on page 10, line 22 of the specification as follows.

The final tablet formulation was selected based on the results of excipient compatibility and antioxidant studies. Table 3 shows the formula used. In order to prevent the slow drug release of high shear granulation, the rhIL-11 tablets using this formula were manufactured by fluid bed granulation method. The tablets were sealed with a layer of HPMC, enteric coated with an aqueous dispersion containing ~~Eudragit~~ EUDRAGIT® L30D, talc and triethyl citrate and sealed again with HPMC.

Amend the paragraph beginning on page 10, line 29 of the specification as follows.

The integrity of rhIL-11 following stresses encountered during the process of tablet manufacturing was investigated. Different compaction forces were used to evaluate the effect of tablet manufacturing stresses on the integrity of rhIL-11. These tablets weighed 150 mg,

contained 2.5 mg of rhIL-11 (lyophilized powder), EXPLOTAB®, microcrystalline cellulose, NU-TAB®, ~~syloid~~ SYLOID® and magnesium stearate. Tablets were directly compressed to hardness of 2.4, 4.0, 7.5, or 12.5 KP. The protein integrity was measured by determining % recovery, % multimer, % Met^{58} oxidized species, % related and specific activity of rhIL-11 by T-10 bioassay. The results in Table 4 show that recovery, % multimer, % Met^{58} oxidized species, and % related did not change for rhIL-11 tablets compressed to varying degrees of hardness. Similarly, the specific activity of various formulation blend and tablets were found within the range of specification (Table 5). This shows that compression force does not cause chemical or physical instability of rhIL-11 in the formulations studied.

Amend the paragraph beginning on page 13, line 21 of the specification as follows.

Table 9 shows the compositions of three sustained release tablets prepared by fluid bed granulation. Fluid bed granulation contain rhIL-11 mixture, ~~Avicel~~AVICEL® PH102, sodium phosphate monobasic, sodium phosphate dibasic, methionine and polysorbate 80. In these studies, the sucrose which was used in the direct compression and high sheer granulation formulations was replaced with mannitol, as sucrose was found responsible for discoloring of the immediate release tablets during storage.

Amend the paragraph beginning on page 14, line 12 of the specification as follows.

Formulation 6 showed a fast initial dissociation rate in 100 mM phosphate medium. Formulation 6 contains ~~Methocel~~ METHOCEL™ K4M PREM as a sustained release polymer. In order to reduce this initial rate of dissolution, higher viscosity grade of HPMC (~~Methocel~~ METHOCEL™ K15 M PREM) was incorporated in the formulation. Tablets of formulations 7 and 8 exhibited improved dissolution behavior. The higher rate of dissolution exhibited by formulation 8 as compared to that for formulation 7 could be due to the disintegrant properties of the extragranular microcrystalline cellulose (~~Avicel~~ AVICEL® PH102), which was not present in the tablets of formulation 7.

Amend the paragraph beginning on page 14, line 23 of the specification as follows.

Prototype formulations which exhibit an optimized release profile for rhIL-11 in 50 mM phosphate medium were prepared and tested. Various formulations were prepared and tested. Monitoring the erosion and dissolution of these formulations indicated that using 20 - 30 % ~~methocel~~ METHOCEL™ K100 LV, LH, CR Premium as a sustained release polymer might lead to obtaining formulations that exhibit an acceptable dissolution behavior. Table 10 shows the compositions of these formulations.